[redacted]

B' Cont

biological modulator of insulin activity, which compound possesses one or more ionic and hydrophobic chemical moieties spatially located so as to mimic the spatial location of at least an ionic [and] or a hydrophobic amino acid residue of insulin, which amino acid is associated with binding of insulin to its receptor.

## REMARKS

### I. The Amendment

The amendments to claim 1 are fully supported in the specification at, for example, (i) page 4, lines 15 through 18, which describes use of non-peptidyl compounds; and (ii) page 26, lines. 18 through 19, which explicitly states that the compounds used in the claimed methods may mimic "any number" of amino acid residues associated with binding of insulin to its receptor. The compound may therefore include a single moiety that mimics a single insulin amino acid, and this consequence necessitates that the penultimate clause be amended to recite an ionic or a hydrophobic amino acid (as opposed to inoic and hydrophobic). The remaining amendments are submitted only to improve clarity of the claimed subject matter. Upon entry of the present amendment, pending claims in the application will read as set out in Appendix A hereto.

The amendments include no new matter.

### II. The Restriction Requirement May Properly Be Withdrawn

In view of the amendment to claim 1, the Applicant submits that the Examiner's basis for issuing a restriction requirement is obviated and therefore the restriction requirement may be withdrawn. The basis for the Examiner's position is stated at page 2 that the two groups of claims represent separate inventions because "the method of Invention II [claims 5-19] has non-peptidyl components." Because of this asserted difference, the Examiner maintained that "the methods [of claims 1 through 4 vs claims 5 through 19] have different steps and different products with different functions."

The Applicants respectfully submit that the amendments to claim 1 obviate the Examiner's underlying basis for alleging that the methods of claims 1 through 4 differ from the methods of claims 5 through 19. As amended, the methods of both assertedly distinct inventions utilize non-peptidyl components, and as a result, the methods of all

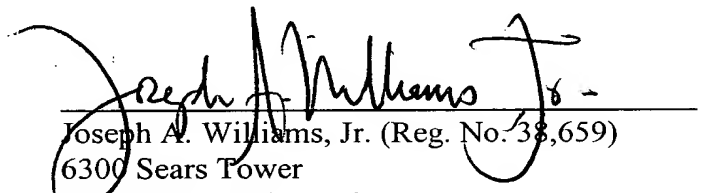
claims in the application may be searched in the same subclass without an undue burden on the Examiner. The Applicants therefore respectfully request that the restriction requirement be withdrawn and all claims 1 through 19 be prosecuted in the present application.

## SUMMARY

The Applicants believe that claims 1 through 19 are in condition for allowance and respectfully request notification of the same.

Respectfully submitted,

MARSHALL, O'TOOLE, GERSTEIN,
MURRAY & BORUN

By 

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## APPENDIX A

1. A method for treating a patient suffering from one or more insulin related ailments, which method comprises the step of: administering to a patient in need thereof a therapeutically effective amount of a non-petidyl compound that is a biological modulator of insulin activity, which compound possesses one or more ionic and hydrophobic chemical moieties spatially located so as to mimic the spatial location of at least an ionic or a hydrophobic amino acid residue of insulin, which amino acid is associated with binding of insulin to its receptor.

2. A method according to claim 1, wherein the ionic amino acid residue is selected from the group comprising: A21 Asn, B21 Glu and A17 Glu.

3. A method according to claim 1, wherein the ionic and hydrophobic amino acid residue(s) is(are) selected from the group consisting of: A21 Asn, B21 Glu, A17 Glu, B24 Phe, B25 Phe, A19 Tyr, B12 Val, B16 Tyr, A2 Ile, A3 Val and A1 Gly.

4. A method according to claim 1, wherein at least one amino acid is selected from the group comprising: A17 Glu, B21 Glu and A21 Asn; and at least one amino acid is selected from the group comprising: B24 Phe, B25 Phe, A19 Tyr, B12 Val and B12 Tyr.

5. A method according to claim 1, wherein the non-peptidyl compound possesses ionic and hydrophobic chemical moieties spatially located so as mimic ionic and hydrophobic residues associated with at least one of the following groups of amino acid residues:

(i.) A21 Asn, B21 Glu, A17 Glu, B24 Phe, B25 Phe;

(ii.) A21 Asn, B21 Glu, B24 Phe, B25 Phe;

(iii.) A21 Asn, B21 Glu, B24 Phe, B25 Phe, A1 Gly, A2 Ile, A3 Val;

(iv.) A21 Asn, B21 Glu, A17 Glu, A19 Tyr, A1 Gly, A2 Ile, A3 Val;

(v.) A21 Asn, B21 Glu, A17 Glu, B12 Val, A1 Gly, A2 Ile, A3 Val;

(vi.) A21 Asn, B21 Glu, B12 Val, A1 Gly, A2 Ile, A3 Val;

(vii.) A21 Asn, B21 Glu, A17 Glu, B16 Tyr, A1 Gly, A2 Ile, A3 Val;

(viii.) A21 Asn, B21 Glu, A17 Glu, A19 Tyr, B12 Val, B16 Tyr;

(ix.) A21 Asn, B21 Glu, A19 Tyr, B12 Val, B16 Tyr;

(x.) A21 Asn, B21 Glu, A17 Glu, B24 Phe, B25 Phe, A19 Tyr, B12 Val, B16 Tyr;

(xi.) A21 Asn, B21 Glu, B24 Phe, B25 Phe, A19 Tyr, B12 Val, B16 Tyr;

(xii.) A21 Asn, B21 Glu, B24 Phe, B25 Phe, B12 Val, B16 Tyr;

(xiii.) A21 Asn, B21 Glu, A17 Glu, B24 Phe, B25 Phe, A19 Tyr;

(xiv.) A21 Asn, B21 Glu, B24 Phe, B25 Phe, A19 Tyr;

(xv.) A21 Asn, A17 Glu, B24 Phe, B25 Phe, A19 Tyr;

(xvi.) B21 Glu, A17 Glu, B24 Phe, B25 Phe, A19 Tyr;

(xvii.) A21 Asn, B21 Glu, A17 Glu, B24 Phe, B25 Phe, B12 Val;

(xviii.) A21 Asn, B21 Glu, B24 Phe, B25 Phe, B12 Val;

(xix.) A21 Asn, A17 Glu, B24 Phe, B25 Phe, B12 Val;

(xx.) B21 Glu, A17 Glu, B24 Phe, B25 Phe, B12 Val;

(xxi.) A21 Asn, B21 Glu, A17 Glu, B24 Phe, B25 Phe, B16 Tyr;

(xxii.) A21 Asn, B21 Glu, B24 Phe, B25 Phe, B16 Tyr;

(xxiii.) A21 Asn, A17 Glu, B24 Phe, B25 Phe, B16 Tyr;

(xxiv.) B21 Glu, A17 Glu, B24 Phe, B25 Phe, B16 Tyr;

(xxv.) A21 Asn, B21 Glu, A17 Glu, B24 Phe, A19 Tyr, B12 Val, B16 Tyr;

(xxvi.) A21 Asn, B21 Glu, B24 Phe, A19 Tyr, B12 Val, B16 Tyr;

(xxvii.) A21 Asn, A17 Glu, B24 Phe, A19 Tyr, B12 Val, B16 Tyr;

(xxviii.) B21 Glu, A17 Glu, B24 Phe, A19 Tyr, B12 Val, B16 Tyr;

(xxix.) A21 Asn, B21 Glu, A17 Glu, B25 Phe, A19 Tyr, B12 Val, B16 Tyr;

(xxx.) A21 Asn, B21 Glu, B25 Phe, A19 Tyr, B12 Val, B16 Tyr;

(xxxi.) A21 Asn, A17 Glu, B25 Phe, A19 Tyr, B12 Val, B16 Tyr; or

(xxxii.) B21 Glu, A17 Glu, B25 Phe, A19 Tyr, B12 Val.

6. A method according to claim 1, wherein the non-peptidyl compound has the following formula:

$AXYXZ_n$ (formula 1)

where A is W or VXW;

V is $V_1$ or $V_2$;

V is substituted with up to two X groups;

$V_1$ is a phenyl or 6 membered heteroaromatic ring, optionally substituted with up to 5 $R_1$ groups, for example but not being limited to benzene, pyridine, pyridazine, pyrimidine, pyrazine, triazine;

$V_2$ is a 5 member ring system which may incorporate up to 4 hetero atoms which may be independently a nitrogen atom, a nitrogen atom optionally substituted with $R_2$, oxygen or sulfur, for example but not being limited to cyclopenta-1,3-diene, pyrrole, furan, thiophene, oxazole, isoxazole, pyrazole, imidazole, thiazole, isothiazole or triazole, the ring system being optionally substituted with up to 4 $R_1$ groups;

W is $W_1$ or $W_2$ or $W_3$;

W is substituted with up to two X groups;

$W_1$ is $V_1$;

$W_2$ is a fused bicyclic ring system comprising rings of 5 or 6 atoms, which may incorporate up to 4 hetero atoms; which may be independently a nitrogen atom, a nitrogen atom optionally substituted with $R_2$, oxygen or sulfur, the system being optionally substituted with up to seven $R_1$ groups and examples include, but are not limited to naphthalene, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, indole, benzothiophene, benzofuran, benzimidazole, indazole, benzoxazole, benzisooxazole, benzthiazole, benzisothiazole, purine, indoline, isoindoline;

$W_3$ is $-N(R_2)R'_2$;

$R_1$ is independently H, OH, alkyl, alkenyl, alkynyl, alkoxy, alkanol, hydroxyalkoxy, haloalkyl, haloalkoxy, halogen, SH, thioalkyl, cyano (-CN),

$N(R_2)R'_2$, phenyl, phenyl optionally substituted with up to five alkyl groups of 1 to 3 carbon atoms or up to five halogen atoms, benzyl, phenethyl, nitro, $-COR_3$, $-R_5COR_3$, $-R_5SOR_3$, $-R_5SO_2R_3$, $-SO_2N(R_2)R'_2$ or azido;

$R_2$ and $R'_2$ are independently H, alkyl of 1 to 6 carbon atoms, alkenyl of 3 to 6 carbon atoms, alkynyl of 3 to 6 carbons, hydroxyalkyl of 2 to 6 carbons, alkoxy of 2 to 6 carbons, haloalkyl, haloalkenyl, haloalkoxy, benzyl, benzyl optionally substituted with up to four $R_1$ groups, phenylethyl, phenylethyl optionally substituted with up to four $_{R_1}$ groups, arylalkyl, and where $R_2$ and $R'_2$ can also be joined to form cyclic structures including, but not limited to pyrrolidine, piperidine, hexahydro-1H-azepine, morpholine or piperazine;

$R_3$ is independently H, OH, alkyl, alkenyl, alkynyl, alkoxy, alkanol, hydroxyalkoxy, $-R_4N(R_2)R'_2$, mesyl, triflouromesyl, $-NHSO_2CH_3$ or $-NHSO_2CF_3$;

$R_4$ is independently a bond, alkyl, alkenyl or alkynyl;

X is independently, a bond, $-R_4N(R_2)R_4-$, $-R_4N{=}NR_4-$, $-R_4N(R_2)-N(R_2)R_4-$, $-R_4OR_4-$, $-R_4SR_4-$, $-R_5-$, $-R_5O-$, $-R_5S-$, $-R_5N(R_2)-$, -SO-, sulfonyl ($-SO_2-$), -CO-, -CONH-, -NHCONH-, -NHCO-, -CONHCO-, $-CON(R_2)-$, $-R_5COR_5-$, $-R_5COR_5N(R_2)R_5-$, $-N(R_2)CO-$ or $-R_4N(R_2)R_4COR_4-$;

$R_5$ is independently alkyl, alkenyl, alkynyl, alkoxy, alkanol, hydroxyalkoxy;

Y is either $Y_1$, $Y_2$ or $Y_3$;

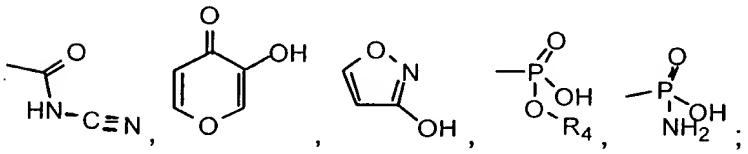
Y is substituted with at least two, but optionally up to four X linking groups;

$Y_1$ is a fused bicyclic ring system comprising rings of 5 or 6 atoms which may incorporate up to 4 hetero atoms, which may be independently a nitrogen atom, a nitrogen atom optionally substituted with $R_2$, oxygen or sulfur, the ring system optionally independently incorporating a sulfoxide (SO), sulfone ($SO_2$) or carbonyl (CO) group and optionally up to seven $R_1$ groups, for example but not limited to croman, isochroman, benzofuran, cromene, 1,2,3,4-tetrahydronaphthalene, 1,4-dihydronaphthalene, indan, indene, benzopiperidine, indoline, isoindoline, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline or pteridine, coumarin or 2,3-dihydrocoumarin;

$Y_2$ is a 6:6:6 or a 6:5:6 fused tricyclic system which may incorporate up to 4 hetero atoms which may be independently a nitrogen atom, a nitrogen atom optionally substituted with $R_2$, oxygen or sulfur, the ring system optionally independently incorporating a sulfoxide (SO), sulfone ($SO_2$) or carbonyl (CO) group, and the ring system being substituted with at least two, but optionally up to four X linking groups and optionally up to seven $R_1$ groups and thus examples include, but are not limited to 9H-xanthone, 9H-xanthene, phenoxathiin, phenoxathiin-10-oxide, phenoxathiin-10-dioxide, acridine, phenazine, phenothiazine, phenoxazine, phenothiazine-5-oxide, phenothiazine-5-dioxide, thiathrene-5-dioxide, thiathrene-5-oxide, carbazole, dibenzo[b,d]furan, dibenzo[b,d]thiophene;

$Y_3$ is $V_1$;

Z is independently $-R_6COOH$, $-R_6SO_3H$, $-R_6NO_2$, $-R_6SO_2H$, $-R_6SO_2NHR_2$; $-R_7SO_2NHCOR_4$ -N-trifluoromesylsulfonamidate, -OH, -2-yl-hydroxyethanoic acid (-CH(OH)COOH), -3-yl-2-hydroxypropanoic acid ($-CH_2CH(OH)COOH$) -2-yl-2-hydroxypropanoic acid ($-CH(CH_3)(OH)COOH$), -3-yl-2,3-dihydroxypropanoic acid (-CH(OH)CH(OH)COOH), -2-yl-2,3-dihydroxypropanoic acid ($-C(CH_2(OH))(OH)COOH$), -3-yl-2-hydroxypropan-3-one-1-oic acid (-COCH(OH)COOH, 2-yl-2-hydroxypropandioic acid ( -C(COOH)(OH)COOH), -2-yl-propandioic acid (-C(COOH)(H)COOH), -4-yl-2-hydroxybutan-4-one-1-oic acid ($-COCH_2CH(OH)COOH$, 2-yl-2-hydroxybutan-1,4-dioic acid ($-C(OH)(COOH)CH_2COOH$), 3-yl-2-hydroxybutan-1,4-dioic acid (-CH(CH(OH)COOH)COOH), 5-yl-tetrazole,



$R_6$ is independently a bond, alkyl, alkenyl, alkynyl, alkoxy, $-CO(CH_2)_n-$, where n is an integer between 0 and 4, alkanoic, alkenoic or alkynoic; with the exception that where $W_1$ is an optionally substituted phenyl then $Y_1$ cannot be an optionally substituted phenyl.

7. A method according to claim 6, wherein the non-peptidyl compound is a dimer or heterodimer wherein the compounds are joined through a X linking group by way of their V or W groups.

8. A method according to claim 6, wherein when V is $V_1$ or $V_2$, then:

$V_1$ is selected from the group consisting of, benzene, pyridine, pyridazine, pyrimidine, pyrazine or triazine and is optionally substituted with up to 5 $R_1$ groups; and

$V_2$ is selected from the group consisting of, cyclopenta-1,3-diene, pyrrole, furan, thiophene, oxazole, isoxazole, pyrazole, imidazole, thiazole, isothiazole or triazole and is optionally substituted with up to 4 $R_1$ groups;

and W is $W_2$ then

$W_2$ is selected from the group consisting of naphthalene, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, indole, benzothiophene, benzofuran, benzimidazole, indazole, benzoxazole, benzisooxazole, benzthiazole, benzisothiazole, purine, indoline or isoindoline and is optionally substituted with up to seven $R_1$ groups;

and Y is either $Y_1$ or $Y_2$ then

$Y_1$ is selected from the group consisting of croman, isochroman, benzofuran, cromene, 1,2,3,4-tetrahydronaphthalene, 1,4-dihydronaphthalene, indan, indene, benzopiperidine, indoline, isoindoline, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline or pteridine, coumarin or 2,3-dihydrocoumarin and is optionally substituted with up to seven $R_1$ groups; and

$Y_2$ is selected from the group consisting of 9H-xanthone, 9H-xanthene, phenoxathiin, phenoxathiin-10-oxide, phenoxathiin-10-dioxide, acridine, phenazine, phenothiazine, phenoxazine, phenothiazine-5-oxide, phenothiazine-5-dioxide, thiathrene-5-dioxide, thiathrene-5-oxide, carbazole, dibenzo[b,d]furan or dibenzo[b,d]thiophene and is optionally substituted with up to seven $R_1$ groups.

9. A method according to claim 6, wherein when A is VXW then:

V is phenyl or pyrazole, optionally substituted with up to 5 $R_1$ groups;

and when A is W or VXW then W is $W_1$, $W_2$ or $W_3$ wherein

$W_1$ is phenyl optionally substituted with up to 5 $R_1$ groups;

$W_2$ is naphthalene or quinoline optionally substituted with up to seven $R_1$ groups wherein $R_1$ is independently H, OH, methyl, ethyl, propyl, nitro, methoxy, ethoxy, 2-hydroxyethoxy, chloro, fluoro or acetyl;

$W_3$ is $-N(R_2)R_2$ wherein $R_2$ is propyl;

X is independently, a bond, methoxy ($-OCH_2-$), oxypropoxy ($-O(CH_2)_3O-$), hexenyloxy ($-O(CH_2)_4CH=CH-$), sulfonyloxy ($-SO_2O-$), methyl ($-CH_2-$), amidyl (-CONH-) or -NHCONH-;

and Y is either $Y_1$ or $Y_2$ then

$Y_1$ is croman, 4-H-chromen-4-one or napthalene optionally substituted with up to seven $R_1$ groups wherein $R_1$ is independently H, OH, methyl, ethyl, propyl, nitro, methoxy, ethoxy, 2-hydroxyethoxy, chloro, fluoro or acetyl;

$Y_2$ is 9H-xanthone optionally substituted with up to seven $R_1$ groups wherein $R_1$ is independently H, OH, methyl, ethyl, propyl, nitro, methoxy, ethoxy, 2-hydroxyethoxy, chloro, fluoro or acetyl;

$Y_3$ is phenyl optionally substituted with up to 5 $R_1$ groups wherein $R_1$ is independently H, OH, methyl, ethyl, propyl, nitro, methoxy, ethoxy, 2-hydroxyethoxy, chloro, fluoro or acetyl; and

Z is independently $-R_6COOH$, $-R_6SO_3H$ or -N-trifluoromesylsulfonamidate wherein $R_6$ is independently a bond or propyl.

10. A method according to claim 6, wherein the non-peptidyl compound is selected from the following group of compounds:

(i.) 4,4'-Methylenebis[3-hydroxy-2-naphthalenecarboxylic acid];

(ii.) 7-[3-(4-acetyl-2-ethyl-5-hydroxyphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

(iii.) 2,4-dichloro-6-(*N*-(trifluoromethanesulfonyl))sulfamoylphenyl 3,5-dichloro-2-hydroxybenzenesulfonate;

(iv.) 7-[(4-acetyl-3-hydroxy-2-propylphenyl)methoxy]-4-oxo-8-propyl-4*H*-1-benzopyran-2-carboxylic acid;

(v.) 7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2*H*-1-benzopyran-2-carboxylic acid;

(vi.) 3,4-dihydro-8-propyl-7-[[3-[2-ethyl-5-hydroxy-4-(1*H*-pyrazol-3-yl)phenoxy]propyl]oxy]-2*H*-1-benzopyran-2-carboxylic acid;

(vii.) 3,4-dihydro-8-propyl-7-[[3-[2-ethyl-5-hydroxy-4- ethoxyphenoxy]propyl]oxy]-2*H*-1-benzopyran-2-carboxylic acid;

(viii.) 3-[4-[7-carboxy-9-oxo-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-9*H*-xanthene]]propanoic acid;

(ix.) 8-propyl-7-(quinol-2'-ylmethoxy)-3,4-dihydro-2*H*-1-benzopyran-2-carboxylic acid;

(x.) 7-(naphth-2'-ylmethoxy)-8-propyl-3,4-dihydro-2*H*-1-benzopyran-2-carboxylic acid;

(xi.) *N*-(trifluoromethanesulfonyl)-3,5-dinitro-4-(*N*',*N*'-dipropylamino)benzenesulfonamide;

(xii.) 8-propyl-7-[3-[4-(4-fluorophenyl)-2-ethyl-5-hydroxyphenoxy]propoxy]-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid;

(xiii.) 3,4-dihydro-7-[[6-(4-methoxyphenyl)hexenyl]oxy]-8-propyl-2H-1-benzopyran-2-carboxylic acid; or

(xiv.) 8,8'-[Carbonylbis[imino-3,1-phenylenecarbonylimino(4-methyl-3,1-phenylene)carbonylimino]]bis-1,3,5-naphthalenetrisulfonic acid.

11. A pharmaceutical composition comprising at least a chemical compound capable of modulating the biological activity of insulin and a pharmaceutically acceptable carrier and/or diluent; wherein said compound has the following general formula.

$$AXYXZ_n \qquad \text{(formula 1)}$$

where A is W or VXW;

V is $V_1$ or $V_2$;

V is substituted with up to two X groups;

$V_1$ is a phenyl or 6 membered heteroaromatic ring, optionally substituted with up to 5 $R_1$ groups, for example but not being limited to benzene, pyridine, pyridazine, pyrimidine, pyrazine, triazine;

$V_2$ is a 5 member ring system which may incorporate up to 4 hetero atoms which may be independently a nitrogen atom, a nitrogen atom optionally substituted with $R_2$, oxygen or sulfur, for example but not being limited to cyclopenta-1,3-diene, pyrrole, furan, thiophene, oxazole, isoxazole, pyrazole, imidazole, thiazole, isothiazole or triazole, the ring system being optionally substituted with up to 4 $R_1$ groups;

W is $W_1$ or $W_2$ or $W_3$;

W is substituted with up to two X groups;

$W_1$ is $V_1$;

$W_2$ is a fused bicyclic ring system comprising rings of 5 or 6 atoms, which may incorporate up to 4 hetero atoms, which may be independently a nitrogen atom, a nitrogen atom optionally substituted with $R_2$, oxygen or sulfur, the system being optionally substituted with up to seven $R_1$ groups and examples include, but are not limited to naphthalene, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, indole, benzothiophene, benzofuran, benzimidazole, indazole, benzoxazole, benzisooxazole, benzthiazole, benzisothiazole, purine, indoline, isoindoline;

$W_3$ is $-N(R_2)R'_2$;

$R_1$ is independently H, OH, alkyl, alkenyl, alkynyl, alkoxy, alkanol, hydroxyalkoxy, haloalkyl, haloalkoxy, halogen, SH, thioalkyl, cyano (-CN), $N(R_2)R'_2$, phenyl, phenyl optionally substituted with up to five alkyl groups of 1 to 3 carbon atoms or up to five halogen atoms, benzyl, phenethyl, nitro, $-COR_3$, $-R_5COR_3$, $-R_5SOR_3$, $-R_5SO_2R_3$, $-SO_2N(R_2)R'_2$ or azido;

$R_2$ and $R'_2$ are independently H, alkyl of 1 to 6 carbon atoms, alkenyl of 3 to 6 carbon atoms, alkynyl of 3 to 6 carbons, hydroxyalkyl of 2 to 6 carbons, alkoxy of 2 to 6 carbons, haloalkyl, haloalkenyl, haloalkoxy, benzyl, benzyl optionally substituted with up to four $R_1$ groups, phenylethyl, phenylethyl optionally substituted with up to four $_{R_1}$ groups, arylalkyl, and where $R_2$ and $R'_2$ can also be joined to form cyclic structures including, but not limited to pyrrolidine, piperidine, hexahydro-1H-azepine, morpholine or piperazine;

$R_3$ is independently H, OH, alkyl, alkenyl, alkynyl, alkoxy, alkanol, hydroxyalkoxy, $-R_4N(R_2)R'_2$, mesyl, triflouromesyl, $-NHSO_2CH_3$ or $-NHSO_2CF_3$;

$R_4$ is independently a bond, alkyl, alkenyl or alkynyl;

X is independently, a bond, $-R_4N(R_2)R_4-$, $-R_4N=NR_4-$, $-R_4N(R_2)-N(R_2)R_4-$, $-R_4OR_4-$, $-R_4SR_4-$, $-R_5-$, $-R_5O-$, $-R_5S-$, $-R_5N(R_2)-$, -SO-, sulfonyl ($-SO_2-$), -CO-, -CONH-, -NHCONH-, -NHCO-, -CONHCO-, $-CON(R_2)-$, $-R_5COR_5-$, $-R_5COR_5N(R_2)R_5-$, $-N(R_2)CO-$ or $-R_4N(R_2)R_4COR_4-$;

$R_5$ is independently alkyl, alkenyl, alkynyl, alkoxy, alkanol, hydroxyalkoxy;

Y is either $Y_1$, $Y_2$ or $Y_3$;

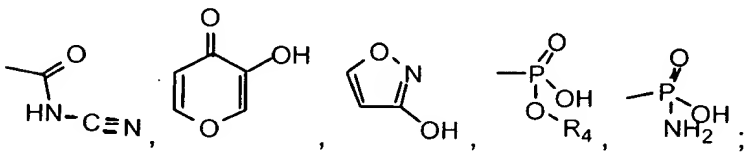
Y is substituted with at least two, but optionally up to four X linking groups;

$Y_1$ is a fused bicyclic ring system comprising rings of 5 or 6 atoms which may incorporate up to 4 hetero atoms, which may be independently a nitrogen atom, a nitrogen atom optionally substituted with $R_2$, oxygen or sulfur, the ring system optionally independently incorporating a sulfoxide (SO), sulfone ($SO_2$) or carbonyl (CO) group and optionally up to seven $R_1$ groups, for example but not limited to croman, isochroman, benzofuran, cromene, 1,2,3,4-tetrahydronaphthalene, 1,4-dihydronaphthalene, indan, indene, benzopiperidine, indoline, isoindoline, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline or pteridine, coumarin or 2,3-dihydrocoumarin;

$Y_2$ is a 6:6:6 or a 6:5:6 fused tricyclic system which may incorporate up to 4 hetero atoms which may be independently a nitrogen atom, a nitrogen atom optionally substituted with $R_2$, oxygen or sulfur, the ring system optionally independently incorporating a sulfoxide (SO), sulfone ($SO_2$) or carbonyl (CO) group, and the ring system being substituted with at least two, but optionally up to four X linking groups and optionally up to seven $R_1$ groups and thus examples include, but are not limited to 9H-xanthone, 9H-xanthene, phenoxathiin, phenoxathiin-10-oxide, phenoxathiin-10-dioxide, acridine, phenazine, phenothiazine, phenoxazine, phenothiazine-5-oxide, phenothiazine-5-dioxide, thiathrene-5-dioxide, thiathrene-5-oxide, carbazole, dibenzo[b,d]furan, dibenzo[b,d]thiophene;

$Y_3$ is $V_1$;

Z is independently -$R_6$COOH, -$R_6SO_3H$, -$R_6NO_2$, -$R_6SO_2H$, -$R_6SO_2NHR_2$; -$R_7SO_2NHCOR_4$ -N-trifluoromesylsulfonamidate, -OH, -2-yl-hydroxyethanoic acid (-CH(OH)COOH), -3-yl-2-hydroxypropanoic acid (-$CH_2$CH(OH)COOH) -2-yl-2-hydroxypropanoic acid (-CH($CH_3$)(OH)COOH), -3-yl-2,3-dihydroxypropanoic acid (-CH(OH)CH(OH)COOH), -2-yl-2,3-dihydroxypropanoic acid (-C($CH_2$(OH))(OH)COOH), -3-yl-2-hydroxypropan-3-one-1-oic acid (-COCH(OH)COOH, 2-yl-2-hydroxypropandioic acid ( -C(COOH)(OH)COOH), -2-yl-propandioic acid (-C(COOH)(H)COOH), -4-yl-2-hydroxybutan-4-one-1-oic acid (-$COCH_2$CH(OH)COOH, 2-yl-2-hydroxybutan-1,4-dioic acid (-C(OH)(COOH)$CH_2$COOH), 3-yl-2-hydroxybutan-1,4-dioic acid (-CH(CH(OH)COOH)COOH), 5-yl-tetrazole,



$R_6$ is independently a bond, alkyl, alkenyl, alkynyl, alkoxy, -$CO(CH_2)_n$-, where n is an integer between 0 and 4, alkanoic, alkenoic or alkynoic;

with the exception that where $W_1$ is an optionally substituted phenyl then $Y_1$ cannot be an optionally substituted phenyl.

12. A pharmaceutical composition according to claim 11, wherein the non-peptidyl compound is a dimers or heterodimers of compounds where such compounds are joined through a X linking group by way of their V or W groups.

13. A pharmaceutical composition according to claim 11, wherein when V is $V_1$ or $V_2$, then:

$V_1$ is selected from the group consisting of, benzene, pyridine, pyridazine, pyrimidine, pyrazine or triazine and is optionally substituted with up to 5 $R_1$ groups; and

$V_2$ is selected from the group consisting of, cyclopenta-1,3-diene, pyrrole, furan, thiophene, oxazole, isoxazole, pyrazole, imidazole, thiazole, isothiazole or triazole and is optionally substituted with up to 4 $R_1$ groups;

and W is $W_2$ then

$W_2$ is selected from the group consisting of naphthalene, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, indole, benzothiophene, benzofuran, benzimidazole, indazole, benzoxazole, benzisooxazole, benzthiazole, benzisothiazole, purine, indoline or isoindoline and is optionally substituted with up to seven $R_1$ groups;

and Y is either $Y_1$ or $Y_2$ then

$Y_1$ is selected from the group consisting of croman, isochroman, benzofuran, cromene, 1,2,3,4-tetrahydronaphthalene, 1,4-dihydronaphthalene, indan, indene, benzopiperidine, indoline, isoindoline, quinoline, isoquinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline or pteridine, coumarin or 2,3-dihydrocoumarin and is optionally substituted with up to seven $R_1$ groups; and

$Y_2$ is selected from the group consisting of 9H-xanthone, 9H-xanthene, phenoxathiin, phenoxathiin-10-oxide, phenoxathiin-10-dioxide, acridine, phenazine, phenothiazine, phenoxazine, phenothiazine-5-oxide, phenothiazine-5-dioxide, thiathrene-5-dioxide, thiathrene-5-oxide, carbazole, dibenzo[b,d]furan or dibenzo[b,d]thiophene and is optionally substituted with up to seven $R_1$ groups.

14. A pharmaceutical composition according to claim 11, wherein in the non-peptidyl compound of formula 1 when A is W or VXW then:

V is phenyl or pyrazole, optionally substituted with up to 5 $R_1$ groups;

and W is $W_1$, $W_2$ or $W_3$ then

$W_1$ is phenyl optionally substituted with up to 5 $R_1$ groups;

$W_2$ is naphthalene or quinoline optionally substituted with up to seven $R_1$ groups wherein $R_1$ is independently H, OH, methyl, ethyl, propyl, nitro, methoxy, ethoxy, 2-hydroxyethoxy, chloro, fluoro or acetyl;

$W_3$ is $-N(R_2)R_2$ wherein $R_2$ is propyl;

X is independently, a bond, methoxy ($-OCH_2-$), oxypropoxy ($-O(CH_2)_3O-$), hexenyloxy ($-O(CH_2)_4CH=CH-$), sulfonyloxy ($-SO_2O-$), methyl ($-CH_2-$), amidyl (-CONH-) or -NHCONH-;

and Y is either $Y_1$ or $Y_2$ then

$Y_1$ is croman, 4-H-chromen-4-one or napthalene optionally substituted with up to seven $R_1$ groups wherein $R_1$ is independently H, OH, methyl, ethyl, propyl, nitro, methoxy, ethoxy, 2-hydroxyethoxy, chloro, fluoro or acetyl;

$Y_2$ is 9H-xanthone optionally substituted with up to seven $R_1$ groups wherein $R_1$ is independently H, OH, methyl, ethyl, propyl, nitro, methoxy, ethoxy, 2-hydroxyethoxy, chloro, fluoro or acetyl;

$Y_3$ is phenyl optionally substituted with up to 5 $R_1$ groups wherein $R_1$ is independently H, OH, methyl, ethyl, propyl, nitro, methoxy, ethoxy, 2-hydroxyethoxy, chloro, fluoro or acetyl; and

Z is independently $-R_6COOH$, $-R_6SO_3H$ or -N-trifluoromesylsulfonamidate wherein $R_6$ is independently a bond or propyl.

15. A pharmaceutical composition according to claim 11, wherein the non-peptidyl compound is selected from the following group of compounds:

(xv.) 4,4'-Methylenebis[3-hydroxy-2-naphthalenecarboxylic acid];

(xvi.) 7-[3-(4-acetyl-2-ethyl-5-hydroxyphenoxy)propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylic acid;

(xvii.) 2,4-dichloro-6-(*N*-(trifluoromethanesulfonyl))sulfamoylphenyl 3,5-dichloro-2-hydroxybenzenesulfonate;

(xviii.) 7-[(4-acetyl-3-hydroxy-2-propylphenyl)methoxy]-4-oxo-8-propyl-4*H*-1-benzopyran-2-carboxylic acid;

(xix.) 7-[3-(4-acetyl-3-methoxy-2-propylphenoxy)propoxy]-3,4-dihydro-8-propyl-2*H*-1-benzopyran-2-carboxylic acid;

(xx.) 3,4-dihydro-8-propyl-7-[[3-[2-ethyl-5-hydroxy-4-(1*H*-pyrazol-3-yl)phenoxy]propyl]oxy]-2*H*-1-benzopyran-2-carboxylic acid;

(xxi.) 3,4-dihydro-8-propyl-7-[[3-[2-ethyl-5-hydroxy-4-ethoxyphenoxy]propyl]oxy]-2*H*-1-benzopyran-2-carboxylic acid;

(xxii.) 3-[4-[7-carboxy-9-oxo-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-9*H*-xanthene]]propanoic acid;

(xxiii.) 8-propyl-7-(quinol-2'-ylmethoxy)-3,4-dihydro-2*H*-1-benzopyran-2-carboxylic acid;

(xxiv.) 7-(naphth-2'-ylmethoxy)-8-propyl-3,4-dihydro-2*H*-1-benzopyran-2-carboxylic acid;

(xxv.) *N*-(trifluoromethanesulfonyl)-3,5-dinitro-4-(*N'*,*N'*-dipropylamino)benzenesulfonamide;

(xxvi.) 8-propyl-7-[3-[4-(4-fluorophenyl)-2-ethyl-5-hydroxyphenoxy]propoxy]-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid;

(xxvii.)3,4-dihydro-7-[[6-(4-methoxyphenyl)hexenyl]oxy]-8-propyl-2H-1-benzopyran-2-carboxylic acid; or

(xxviii.) 8,8'-[Carbonylbis[imino-3,1-phenylenecarbonylimino(4-methyl-3,1-phenylene)carbonylimino]]bis-1,3,5-naphthalenetrisulfonic acid.

16. A method for identifying a non-peptidyl compound possessing ionic and hydrophobic chemical moieties spatially located so as to mimic particular ionic and hydrophobic amino acid residues of insulin which are associated with the binding of insulin to its receptor, said method comprising the steps of: (1) comparing the three dimensional structure of the non-peptidyl compound with a three dimensional pharmacophore of an active site of insulin; and (2) selecting a non-peptidyl compound with ionic and hydrophobic chemical moieties spatially located so as to mimic said site

17. A method for determining whether a non-peptidyl compound identified according to the method of claim 16 is an agonist or an antagonist, said method comprising the step of: exposing the compound to an insulin or insulin like receptor and measuring the change in biological activity following exposure of the compound to the receptor.

18. A method according to claim 1 as substantially herein before described.

19. A pharmaceutical composition according to claim 11 as substantially herein before described.